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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SINGH, ANOOP KUMAR

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/759,734	GEPSTEIN ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-195* is/are pending in the application.

4a) Of the above claim(s) *1-175,182-185 and 190-193* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *176-181,186-189,194 and 195* is/are rejected.

7)☒ Claim(s) *179-181* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/4/2005*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Examiner Singh. The telephone number is provided at the end of this office action.

Election/Restrictions

Applicant's election of claims 176-195 (group IV) in the reply filed on August 17, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicants also elected cardiac specific electrical activity for claims 177 and 189 for first action on merit.

Claims 1-175 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 17, 2006. It is noted that claims 182-185 and 190-193 are drawn to nonelected subject matter. Therefore, claims 182-185 and 190-193 are also withdrawn because they are drawn to non-elected species.

Claims 176-181, 186-189 and 194-195 that are directed to an *in-vitro* culture of isolated human cells which will display substantial proliferation for at least as long as a time period selected from the range of 1-35 days, and which will predominantly display

at least one characteristic associated with a cardiac phenotype of cardiac specific electrical activity for at least as long as a time period selected from the range of 1-60 days would be examined in the instant application.

Claims 176-181, 186-189 and 194-195 are under examination.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc. In the instant case, legal language "said" cannot be used in the abstract (lines 4, 6, 7 and 9). Appropriate correction is required.

Claim Objections

Claims 179-181 are objected to because of the following informalities: Claims 179-181 as recited are dependent on a method claim 178. However, It is noted that claim 178 is not a method claim; rather it is directed to a composition claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 176-181, 186-189 and 194-195 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 176-181, 186-189 and 194-195 are vague and indefinite because it recite term “substantial proliferation” which is subject to variable interpretation depending on Artisan. Since, different isolated human cells will have different proliferative capacity and thus what may be substantial in one cell type may not be substantial in another. Therefore, meets and bound of term substantial cannot be determined. The term "substantial" in claims 176 and 189 is a relative term, which renders the claim indefinite. The term " substantial " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. In the instant case, it is

unclear "substantial proliferation" is relative to what? Furthermore, it is also unclear to an extent it recite an inherent property of all cells that they proliferate from a single cell for at least 1 day. In addition claim 176, also recite a limitation "predominantly" displays at least one characteristic. However, it unclear what percentage or number of cells are considered predominantly. Furthermore, the ranges for proliferation (1-35 days) and cardiac phenotype (1-60) are inconsistent and confusing in claims 176. It is further unclear whether cardiac phenotype as recited in claims 176 and 188 are with respect to any disease or experimental condition. Claims 177-181, 168-189 and 194-195 directly on indirectly depend on claim 176. Appropriate correction is required.

The term "slow conduction" in claims 188 and 195 is a relative term, which renders the claim indefinite. The term "slow" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. In the instant case, it is unclear "slow conduction" is relative to what? Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 176-181, 186-189 and 194-195 are rejected under 35 U.S.C. 102(a) as being anticipated by Kehat et al (Circulation, Supplement II, Vol. 102 N0. 18, October 31, 2000, abstract IDS).

Kehat et al teach plating of human embryoid bodies containing cardiomyocytes tissue on gelatin coated microelectrode array containing 60 electrodes spaced 100 μM apart to record at a sampling rate of 25MKz for up to 50 days post plating. Yeder et al determined a stable pacemaker position with mean firing rate of 1.57. It is noted that activation spread and velocity were stable during consecutive beats and recording days. Kehat conclude that these studies provide evidence that cardiomyocytes differentiating from human ES cell are able to form an excitable media because of in vitro cell-to-cell interaction. Thus, Kehat et al teach an *in vitro* culture of cardiomyocytes that maintains cardiac phenotype for at least up to 50 days and shows cardiac specific rhythmic electrical activity. Since, Kehat et al taught an *in vitro* culture of human cell of cardio specific linage obtained from human ES cell that shows the cardiac specific rhythmic activity. The cardio specific linage of human cell disclosed by Kehat and those embraced by the instant claims appear to be structurally same, therefore, proliferation potential and cardiac phenotype of these cells will remain inherent property of these

cells. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior ad products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433.

Claims 176-177, 186-189 and 194-195 are rejected under 35 U.S.C. 102(b) as being anticipated by Itskovitz-Eldor et al (Mol Med. 2000 Feb;6(2):88-95, IDS).

Itskovitz-Eldor et al teach induction of expression of cell-specific genes during differentiation of the human ES cells into embryoid bodies (EB). It is noted that Itskovitz-Eldor et al disclose differentiation of human ES cell in myocardial linage that is induces development of pulsing muscle in EB (see page 92, col. 2, para 2). Itskovitz-Eldor et al also disclose a large vacuolated EB including cardiac muscle cell layer that is pulsing in synchronous rhythm (see Figure 4 A and B). It is further noted that Itskovitz-Eldor further characterizes the differentiated ES cell by dissociating EB with trypsin and plated cell on monolayer. Since, Itskovitz-Eldor et al taught an *in vitro* culture of human cell of cardio specific linage obtained from human ES cell that shows the cardiac specific

synchronous rhythmic activity. The cardio specific linage of human cell disclosed by Itskovitz-Eldor and those embraced by the instant claims appear to be structurally same, therefore, proliferation potential and other cardiac phenotype of these cells will be inherently present in the cells disclosed by Itskovitz-Eldor. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior ad products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433.

Where, in the instant cases, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

Claims 176-177, 186-189 and 194-195 are rejected under 35 U.S.C. 102(e) as being anticipated by Xu et al (US 2005/0164382A1, dated 7/28/2005, effective filing date 7/12/2001).

Xu et al disclose human cells of the cardiomyocyte lineage. The cells are obtained by from the cultures of pluripotent stem cells to differentiate in vitro, and then harvesting cells differentiated cells showing morphologic markers characteristic of cardiomyocytes, and spontaneous periodic contraction (see abstract). It is noted that Xu et al teach that the harvested aggregates of EB are plated onto a solid substrate, and cultured for a period that allows cells within the aggregates to adopt a cardiomyocytes phenotype in at least 8 days, or within 10 or 12 days (see paragraph 91). Xu et al contemplate characterizing these cells by using various cardiac specific marker including Cardiac troponin T, atrial natriuretic factor, GATA-4 and spontaneously contracting cells (see paragraph 114-135). Thus, it is clear that Xu et al teach an in vitro culture of isolatd human cell that displays characteristics with cardiac phenotype. Since, Xu et al taught an *in vitro* culture of human cell of cardio specific linage obtained from human ES cell that shows the cardiac specific contractile activity. The cardio specific linage of human cell disclosed by Xu and those embraced by the instant claims appear to be structurally same, therefore, proliferation potential and other cardiac phenotype associated with these cells will be inherently present in these cells. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15

USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior ad products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 176-181, 186-189 and 194-195 are rejected under 35 U.S.C. 103(a) as being unpatentable over Itskovitz-Eldor et al (Mol Med. 2000 Feb;6(2):88-95, IDS) and Igelmund et al (Pflugers Arch. 1999 Apr;437(5):669-79).

Itskovitz-Eldor et al teach induction of expression of cell-specific genes during differentiation of the human ES cells into embryoid bodies (EB). It is noted that Itskovitz-Eldor et al disclose differentiation of human ES cell in myocardial linage that is induces development of pulsing muscle in EB (see page 92, col. 2, para 2). Itskovitz-Eldor et al also disclose a large vacuolated EB including cardiac muscle cell layer that is pulsing in synchronous rhythm (see Figure 4 A and B). It is further noted that Itskovitz-Eldor further characterizes the differentiated ES cell by dissociating EB with trypsin and plated cell on monolayer. Since, Itskovitz-Eldor et al taught an in vitro culture of human cell of cardio specific linage obtained from human ES cell that shows the cardiac specific synchronous rhythmic activity. The cardio specific linage of human cell disclosed by Itskovitz-Eldor and those embraced by the instant claims appear to be structurally same, therefore, proliferation potential and cardiac phenotype of these cells will be inherent property of the cells. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior ad products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433. However, Itskovitz-Eldor et al do not

explicitly teach a method to culture cell in contact with a multi electrode array for monitoring cardiac electrical activity.

Prior to instant invention, Igelmund et al (Pflugers Arch. 1999 Apr; 437(5): 669-79) teach a method to investigate the spontaneous electrical activity of cardiomyocyte clusters in EBs, of small groups of cells, and of single cardiomyocytes (see page 670, col. 1, lines 2-4). Igelmund et al disclose that single embryoid bodies are plated for multiple recording from several locations of individual EBs (Figure 1). The electrode matrix consisted of 60 TiN-coated gold electrodes with a diameter of 10 or 30 µm, arranged in eight columns and eight rows with a distance of 100 or 200 µm between adjacent electrodes (see Figs. 4, 5) (see page 670, column 1, extracellular recording section). Igelmund et al teach that by recording population action potentials from the beating areas of EB, one could determine the electrical interaction between cardiomyocytes and beating activity (see page 677, paragraph 2). Igelmund et al conclude that this method of field potential recordings from clusters of ES cell-derived cardiomyocytes within EBs provide a useful tool for studying in vitro chronotropy and action potential propagation (see page 678, column 1, paragraph 2). However, Igelmund et al do not explicitly teach recording action potential of human cells.

Accordingly, in view of the teachings of Igelmund et al and Itskovitz-Eldor, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the method of Igelmund et al by replacing the mouse ES cells to human cells disclosed by Itskovitz-Eldor in order to determine the electrical interaction between cardiomyocytes and beating activity of human cardiomyocytes.

Igelmund had already taught a method to use multiple recording from several locations of individual EBs using electrode matrix to determine the action potential from the beating areas (*supra*). In addition, at the time of filing of this application cardiomyocytes differentiated from embryonic stem cell of different species were also known in the art as taught by Itskovitz-Eldor and Igelmund et al and discussed above. The skilled artisan would be motivated to replace the mouse cardiomyocytes with human cell since, action potential recordings from clusters of ES cell-derived cardiomyocytes within EBs would have provided in vitro chronotropy and action potential propagation of these cells for their potential use in transplantation medicine.

One who would practiced the invention would have had reasonable expectation of success because Igelmund et al had already taught the method of extracellular recordings of the population action potentials of cardiomyocyte clusters to perform long-term recordings (for up to several weeks) from individual EBs under cell culture conditions. Itskovitz-Eldor taught human cardiomyocytes linage cells that are obtained from human ES cell showing cardiac phenotype. Igelmund et al had had already described the use of multiple electrode array system to map the beating area ofs with electrical activity. Thus, it would have only required routine experimentation to replace the mouse cell with human cardiomyocytes obtained from human ES cell to determine the action potential of pulsating cardiomyocytes as disclosed by Itskovitz-Eldor.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272- 0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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